REMARKS

Claims 97-99, 101-111 and 113-118 are pending in the application. Applicants have herein above amended independent claims 97, 111, and 113. Claims 98 and 99 are canceled without prejudice in light of the amendments to claims 97, 111 and 113. The claim amendments are completely supported by the application as originally filed, and thus they do not involve any issue of new matter. Therefore, entry of this amendment is respectfully requested such that claims 97, 101-111 and 113-118, as amended, will be pending.

Applicants appreciate the courtesies extended by the Examiner during a telephone conference with their representative, John P. White, Esq. (Reg. No. 28,678), on March 26, 2002. The remarks set forth herein are in accordance with the matters discussed during the subject telephone conference.

Based on the telephone conference, it is applicants' understanding that this amendment is to be filed in the Office by telefacsimile, and that the Examiner will give this response an expedited review. Following such review it is applicants' further understanding that the Examiner will permit an interview with applicants' counsel to discuss, inter alia, the above amendments in an effort to resolve any remaining issues concerning the patentability of the claims of the present case, which issues may also be relevant to several pending related applications by the same inventors. If this understanding is not correct, the Examiner is respectfully requested to telephone applicants' representative at the number below to clarify any such misunderstanding.

Applicants note with appreciation the statement in ¶5 on p.2 of the Office Action that the rejection of claims 97-99 and 101-118 under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, is withdrawn in light of the amendments previously made to the claims.

Objection to the Disclosure

The Examiner stated that the prior objection to the disclosure is maintained for the reasons set forth in the Office Action mailed June 18, 1998 (Paper No. 16). The Examiner further stated that applicants submit they will provide a new Figure 6B to overcome the rejection when the case is in condition for allowance. The Examiner additionally stated that until applicants submit a proper Figure, the objection is maintained.

In response, applicants will provide a new Figure 6B upon the indication of allowable subject matter.

Obviousness Type Double Patenting Rejection

The Examiner provisionally rejected claims 97-99, 101-111 and 113-118 as being unpatentable due to obvious-type double patenting over claims 78-92 and 94-99 of copending Application No. 08/477,097 for the reasons made of record in Paper No. 20 mailed October 6, 1999, and Paper No. 22, mailed June 27, 2000. The Examiner stated that applicants' arguments filed August 1, 2001, i.e., that the claims of Application No. 08/477,097 do not render obvious the instant claims, have been fully considered but are not persuasive because applicants

have provided no reasoning to dispute the obviousness set forth in the previous Office Actions.

The Examiner has additionally provisionally rejected claims 97-99, 101-111 and 113-118 as being unpatentable due to obviousness-type double patenting over pending claims 78-93 and 95-100 of copending Application No. 08/475,084 [Sic. 08/475,784] for the reasons made of record in Paper No. 20, mailed October 6, 1999 and Paper No. 22, mailed June 27, 2000. The Examiner stated that applicants' arguments filed August 1, 2001, i.e., that the claims of 08/475,784 do not render obvious the instant claims, have been considered but are not persuasive because applicants have provided no reasoning to dispute the obviousness set forth in previous Office Actions.

In a new ground of rejection, as set forth in ¶11 on p.12 of the Office Action, claims 97-99, 101-111 and 113-118 are provisionally rejected as being unpatentable due to obviousness-type double patenting over claims 109-122 of copending Application No. 08/477,147. The Examiner stated that, although the claims are not identical, they are not patentably distinct from each other because the claims of Application No. 08/477,147 also encompass the same composition as that which is instantly claimed (i.e., a conjugate comprising a ganglioside derivative with an altered ceramide portion conjugated to an immunogenic protein based carrier, a saponin and a pharmaceutically acceptable carrier), and a method of treatment using such.

The provisional double-patenting rejections of claims 97-99, 101-111 and 113-118 of the present application over applications Serial No. 08/477,097; 08/475,784 and 08/477,147 are maintained. In response to these rejections,

applicants submit that M.P.E.P. §804 IB, in discussing provisional double-patenting rejections between copending applications, requires that the:

> 'provisional' double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that 'provisional' double patenting rejection is the only rejection remaining in one of the applications. If the 'provisional' double patenting rejection in one application is the only rejection remaining in the application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the 'provisional' double patenting rejection in the other application into a double patenting rejection at the time one application issues as a patent. (emphasis supplied by applicants).

Applicants submit, therefore, for the reasons discussed below, that the claim amendments made herein to claims 97, 111 and 113 are believed to overcome the §103(a) rejection of those claims, as well as the claims which depend therefrom, which rejections should therefore be withdrawn. Following such withdrawal of the §103(a) rejections, the only remaining rejection in this application would be the provisional double patenting rejection of claims 97-99, 101-111 and 113-118. In accordance with the M.P.E.P. section quoted above, the provisional double patenting rejection should thus be withdrawn to permit the application to issue as a patent. Such action is therefore respectfully solicited.

Rejection Under 35 U.S.C. 103 (a)

The Examiner stated that the prior rejection of claims 97-99, 101-111 and 115-118 under 35 U.S.C. §103(a) as being unpatentable over Livingston et al (Cancer Research, 149:7045-7050,1989) in view of Ritter, et al. (Seminars in Cancer Biology, 2:401-409, 1991), Liane et al. (Journal of Biological Chemistry, 249 (14):4460-4466, 1974), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol, 812:32-43, 1990), Kensil et al. (The Journal of Immunology, 146(2):431-437, 1991), Marciani et al. (Vaccine, 9:89-96, 1991) and Uemura et al. (J. Biochem, 79(6):1253-1261, 1976) is maintained for the reasons made of record in the "previous Office Actions". The Examiner then reiterated these reasons as follows.

Examiner's summary of bases for claim rejections:

The Examiner stated that Livingston et al (Cancer Research) teach a composition administered to melanoma patients for stimulating the production of antibodies directed against a carbohydrate epitope on the ganglioside GM2 (page 7046-7048). The Examiner stated that Livingston et al. teach that the composition for treatment is administered at concentrations of 100, 200 or 300 µg with an adjuvant, Bacillus-Calmette-Geurin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline, p. 7046, column 1, paragraph 3, and paragraph bridging p. 7046-7047.). The Examiner stated that Livingston et al. teach that melanoma recurrence was delayed in patients developing GM2 antibodies after treatment with the composition (page 7048, paragraph 1 and column 2, paragraph 2). The Examiner stated that Livingston et al. teach that more patients produce IgM antibodies than IgG antibodies to the GM2 (page 7047, paragraph bridging columns 1-2). The Examiner also

stated that Livingston et al. also teach the gangliosides GM2, GD2 and GD3 are expressed on the cell surface of human malignant melanomas (page 7045, column 1, paragraph 2) and that Livingston et al. differ [i.e., from the present invention] by not teaching the conjugation of the GM2 or other gangliosides by means of a carbon on the ceramide moiety with aminolysyl groups on Keyhole Limpet Hemocyanin (KLH) in a composition and using this composition for treatment.

The Examiner further stated that Ritter et al (1991) teach that IgG response to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the ganglioside, resulting the in the T cell help necessary for the response (page 406, paragraph 1). The Examiner stated that Ritter et al. teach that the advantage of including an IgG antibody response (vs IgM) against gangliosides is that IgG: a) has a higher affinity, b) is better able to penetrate solid tissues, c) is able to mediate antibody-dependent cell-mediated cytotoxicity, and d) is generally detectable in the serum for longer periods after immunization.

The Examiner additionally stated that Liane et al. (Journal of Biological Chemistry, 249(14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose or the amino group-bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e., the instant carbon double bond of ceramide) and coupling of the carboxyl bearing product to the amino group of aminoethyl agarose or the amino group-bearing glass beads.

The Examiner also stated that Ritter et al. (1990) teach that GD3 lactone is more immunogenic than GD3.

The Examiner additionally stated that Livingston et al. (U.S. Patent No. 5,102,663) teach that gangliosides GM3, GM2, GD3, GD2, GT3 and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin (column 1, lines 22-28).

The Examiner further stated that Kensil et al. teach that QS-21 (i.e., the instant carbohydrate derivable from the bark of a Quillaja saponaria Molina tree) produced a higher antibody response than conventional aluminum hydroxide (page 433, column 2, paragraph 4, and Figure 3). Kensil et al. also teach that the immune responses obtained with QS-21, reached a plateau at doses between 10-80 µg in mice (page 433, column 1, paragraph 3).

The Examiner additionally stated that Marciani et al. teach the use of QS-21 adjuvant was useful because it did not cause toxic reaction in cats (page 93, paragraph 1).

The Examiner additionally stated that Uemura et al. (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity of the ganglioside derivative with antibodies.

The Examiner therefore stated that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the composition taught by Livingston et al. by conjugating the GM2 to KLH by covalently coupling GM2 to KLH by substituting GM2 for the globoside and KLH for aminoethyl agarose to produce a GM-2-KLH conjugate by means of the olefinic bond of the sphingosine moiety of the GM2 (i.e., the instant ceramide double bond) and the ε-aminolysyl groups present in the KLH protein using the method

of Liane et al. (emphasis supplied by applicants) and to add QS-21 as an adjuvant to the GM2-KLH conjugate for use as a vaccine because the conjugated composition would be expected to enhance the IgG response to the ganglioside, as taught by Ritter et al. (1991), thus providing the advantages by Ritter et al. (1991) and adding the QS-21 would be advantageous because it provides for a higher antibody response that the commonly used adjuvant used by Kensil et al. and QS-21 provides the advantages that it is not toxic to animals as is taught by Marciani et al.

The Examiner therefore stated that it would also have been *prima facie* obvious to use doses of between 10 and 80 µg of QS-21 in the composition and to optimize the dose accordingly because the immune response with QS-21 plateaus at doses between 10-80 ug and optimization of the weight ratio of the components of the composition to provide an optimal response is well within the ordinary skill in the art as is use the composition as modified supra for treatment of melanoma as taught by Livingston et al. (Cancer Research).

The Examiner additionally concluded that it would also have been *prima facie* obvious to one of ordinary skill in the art to substitute any one of GM3, GD2, GD3, or σ-acetyl GD3 for the GM2 ganglioside in the composition and method as combined, supra, because they are all prominent cell-membrane components of melanomas as taught by Livingston et al. (U.S. Patent No. 5,102,663) and one of ordinary skill in the art would know they react with the melanoma cells.

The Examiner further stated that it would also have been prima facie obvious to one of ordinary skill at the time the invention was made to substitute the GD3 lactone for the GM2

ganglioside in the composition because GD3 lactone is more immunogenic than GD3, as taught by Ritter et al. (1990) and would be expected to product an enhanced antibody response as compared to GD3.

The Examiner further stated that optimization of the dosage, the route of immunization, and the number of sites of immunization to administer the composition, are well within the skill of the ordinary artisan.

The Examiner further stated that one would have reasonably expected the conjugation procedure to work as substituted because conjugation through the ε-aminolysyl groups of carrier proteins for enhanced immunogenicity is routine in the art and Uemura et al. (J Biochem, 79(6):1253-1261, 1976) teach that the ozonolysis and reduction of various sphingolipids did not affect the haptenic reactivity with antibodies.

Examiner's analysis of arguments made by applicants to claim rejections in their August 1, 2001 response:

The Examiner stated in the Office Action that applicants argue that the references do not teach, suggest or disclose applicants invention. The Examiner further stated that specifically, applicants' argue that the primary reference, Livingston et al. (1989) fails to teach conjugation of GM2 or other gangliosides by means of a carbon on the ceramide moiety with aminolysyl groups on KLH in a composition, or using this conjugate for treatment, and that applicants further argue that the secondary references fail to supply this teaching.

The Examiner stated that with regard to Ritter et al. (1991), applicants acknowledge that Ritter et al. (1991) teaches conjugation of GM2 to KHL. The Examiner further stated that

applicants argue that Ritter et al. (1991) fails to teach the chemical nature of the GM2-KLH conjugate, or how to make the conjugate, and further that the reference does not disclose conjugation through the ceramide.

The Examiner additionally stated that with regard to Ritter et al. (1990), applicants argue that there is no teaching of conjugation to KLH, and further, that modifications of the gangliosides of Ritter et al. (1990) are in the carbohydrate portion, not the ceramide portion, such that Ritter et al. (1990) teach away from ceramide conjugation.

The Examiner additionally stated that with regard to Liane et al., applicants supplied Helline et al., which applicants argue teaches that Liane et al. method "is of limited use for the conjugation of ganglioside to carrier proteins because it requires acetylated, methyl ester derivatives of gangliosides to avoid coupling via the sialic acid carboxyl group. Deacylation after conjugation under basic conditions is necessary, conditions most proteins cannot be exposed to without degradation". The Examiner stated that, based on this teaching, applicants concluded that Liane et al. fails to supply the missing teachings of the primary reference. The Examiner further stated that with regard to the other secondary references (Uemura et al., Kensil, et al., Marciani et al., and Livingston et al. (U.S. Patent 5,102,663)) applicants argue that these references fail to teach a ceramide linkage.

The Examiner went on to state that applicants' arguments filed August 1, 2001 in response to these grounds for rejection have been fully considered but they are not persuasive.

Examiner's response to applicants' arguments in their August 1, 2001 response:

Responding to applicants' arguments in their August 1, 2001 response (see, e.g., pp.10-16 of the subject Amendment, which remarks will not be repeated here), the Examiner stated in the present Office Action that the conjugate and method of treatment taught in Livingston et al. teaches the instantly claimed conjugate, but fails to teach conjugation to KLH.

The Examiner further stated in the Office Action that Ritter et al. (1991) teaches that the conjugation of GM2 to KLH is desirable because it generates a superior immune response, and that with regard to Ritter et al. (1991), applicants' argument that the reference fails to teach the specific ceramide conjugation is not persuasive because such a conjugation was known in the art at the time the invention was made (as set forth in the additional secondary references). The Examiner additionally stated that the key teaching of Ritter et al. (1991) is that one would expect a superior immune response when GM2 is coupled to KLH. The Examiner stated that Ritter et al. (1991) provides motivation to conjugate the ganglioside to KLH.

The Examiner stated that, with regard to Ritter et al. (1990), applicant's arguments misrepresent the teachings of Ritter et al.(1990) and the examiner's reasons for citing such. According to the Examiner, Ritter et al. (1990) was cited for the teaching that GD3 lactone is more immunogenic that GD3 and that the reference was not cited to represent ceramide linkage.

The Examiner additionally stated that in contrast to the

 Liane et al. does not require

deacetylation after conjugation. The Examiner stated that it appears that the reaction that applicants had referred to is that of figure 2 in the Liane et al. paper, in which the deacetylation step occurs after glass beads have been conjugated to the ganglioside. The Examiner in her remarks then pointed applicants to figure 1 of Liane et al., which contains a different reaction, i.e., one which provides carbodiimide linkage under standard acidic, not basic conditions. The Examiner stated that the deacetylation step in the conjugation method of figure 1 occurs before the linkage step and the protein is not present in basic conditions when substituted for the sepharose. The Examiner further stated that carbodiimides under conditions of Liane et al. have long been used for the coupling of peptides to carrier proteins and will not degrade the protein, and that with regard to the other secondary references (Uemura et al., Kensil et al., Marciani et al. and Livingston et al. (U.S. Patent 5,102,663)) that applicants only argue that these references fail to teach a ceramide linkage. The Examiner stated, however, that they (i.e., the secondary references) are not cited for the teaching of a ceramide linkage. The Examiner thus stated that the rejection is maintained for reasons of record.

The eight reference cited in combination to reject claims 97-99, 101-111, 113 and 115-118 under 35 U.S.C. §103(a) are all extensively discussed by applicants in their submission filed August 1, 2001 (see, e.g., pp 12-16 of the August 1, 2001 submission). Those discussions, which applicants believe provide sufficient grounds for distinguishing the invention over the cited references, will not be repeated here. However, the substance of the subject arguments is expressly incorporated into this response by reference thereto.

Responding, therefore, to the grounds for rejection as summarized by the Examiner in the present Office Action, Applicants respectfully traverse the Examiner's rejection that the invention recited in the claims is obvious over the cited art. Applicants respectfully disagree with the Examiner's contention that the conjugation procedure described by the references as combined provides the same procedure as applicants' presently claimed coupling procedure. Applicants contend that the cited references, namely Livingston et al. (Cancer Research) in view of Ritter et al. (Seminars in Cancer Biology), Liane et al.(Journal of Biological Chemistry), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (Immunobiol), Kensil et al. (The Journal of Immunology), Marciani et al. (Vaccine) and Uemura et al. (J. Biochem) do not teach, suggest, or otherwise disclose applicants' claimed invention and therefore these references, in combination, do not render obvious the claimed invention.

In support of their position, Applicants submit that the presently pending independent claims of the application (nos. 97,111, and 113) are now amended to recite, respectively a composition and methods involving administration of the composition, wherein the composition comprises: a) a conjugate of i) a GM2 ganglioside derivative which comprises an unaltered oligosaccharide part and an altered ceramide portion comprising a sphingosine base, to ii) Keyhole Limpet Hemocyanin, comprising an ε-aminolysyl group; b) a saponin derivable from the bark of a Quillaja saponaria Molina tree; and c) a pharmaceutically acceptable carrier; the relative amounts of such conjugate and such saponin being effective to stimulate or enhance antibody production in a subject, **wherein in the conjugate the ganglioside derivative is covalently** [illegible] **pet Hemocyanin through a C-4 carbon of**

the sphingosine base of the ceramide portion of the ganglioside derivative to the ε-aminolysyl group of Keyhole Limpet Hemocyanin, wherein the C-4 carbon is present in a CH_2 group. [Emphasis added].

As noted by the Examiner in the paragraph bridging pp.5-6 of the present Office Action, Liane et al,. (Journal of Biological Chemistry, 294 (14):4460-4466, 1974) teach a method for covalent coupling of gangliosides to aminoethyl agarose or amino group-bearing glass beads by oxidative ozonolysis of the olefinic bond of the sphingosine moiety (i.e., the instant carbon double bond of the ceramide) and coupling of the carboxyl bearing product to the amino group bearing glass beads.

On p. 10 of the Office Action, the Examiner specifically points applicants to Figure 1 of the Liane, et al. reference (see p.4461). As illustrated therein the ganglioside is coupled to the amino group through a C-4 carbon which forms part of a C=O group.

In contrast, and as now specifically recited in independent claims 97, 111 and 113 of the present application, the ganglioside derivative of the composition of the present invention is covalently bound, i.e. conjugated, to the Keyhole Limpet Hemocyanin, through a C-4 carbon of the sphingosine base of the ceramide portion of the ganglioside derivative to the ε-aminolysyl group of Keyhole Limpet Hemocyanin, wherein the C-4 carbon is present in a CH_2 group. [emphasis added].

The above-described linkage is clearly illustrated in Figure 1-2 of the present application wherein the C-4 carbon through

which the covalent bonding occurs forms part of a CH_2 group, and not a C=O group as in the case of the Liane, et al. reference. As the presently claimed mode of linkage is neither taught nor even suggested by the Liane et al. reference, nor any of the other references cited in combination to rejection claims 97, 101-111, 113 and 115-118, applicants respectfully submit that the invention as now recited in the (amended) independent claims, as well as the claims which depend therefrom, is not obvious to one of ordinary skill in the art. Thus, the rejection of claims 97, 101-111, 113 and 115-118 under 35 U.S.C. §103(a) should be withdrawn. Claims 98-99 have been canceled (without prejudice) as noted above.

Rejection Under 35 U.S.C. §103(a)

The prior rejection of claim 114 under 35 U.S.C. §103(a) as being unpatentable over Livingston et al. (Cancer Research), Ritter et al. (Cancer Biology, 1991), Liane et al. (Journal of Biological Chemistry, 249 (14);4460-4466 (1974), Livingston et al., (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al. and Marciani et al. and Uemera et al. (J. Biochem., 79(6):1253-1261, 1976) as applied to claims 97-99, 101-111, 113 and 115-118, and further in view of Irie et al. (U.S. Patent No. 4,557,931) is maintained by the Examiner, for reasons of record "in previous Office Actions" and which were reiterated as follows.

The Examiner stated that the combination differs by not teaching the administration of the composition for treating cancer of epithelial origin.

With regard to the patent to Irie et al., the Examiner stated that Irie et al. teaches that the ganglioside GM2 is found on

or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31).

The Examiner concluded in the Office Action that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer the GM2-KHL conjugate/QS-21 composition or other ganglioside conjugate/QS-21 composition as combined *supra* to patients afflicted with or susceptible to a recurrence of cancer of an epithelial origin (i.e. breast carcinomas) because the ganglioside GM-2 is found in the stroma of the tumor as taught by Irie et al. and one of ordinary skill in the art would expect that the antibodies produced by the composition react with the tumor and treat the disease.

The Examiner noted that Applicants argue that Irie et al. does not supply the missing teaching of a ceramide linkage and that Applicants arguments filed August 1, 2001 have been fully considered but they are not persuasive.

The Examiner further stated that the teaching of a ceramide linkage is not missing, and Irie et al. is not relied upon to teach such. The Examiner additionally stated that Irie et al. teach that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas (column 1, lines 28-31) and that Applicants have provided no arguments for such. The Examiner thus stated that the rejection is maintained for the reasons of record.

Applicants respectfully traverse the rejection of claim 114 in that claim 114 is dependent from claim 113 which, as discussed above, is clearly distinguishable over the combination of Livingston et al., Ritter, et al. (Seminars in Cancer Biology, 1991), Liane et al.), Livingston et al. (U.S. Patent No. 5,102,663), Ritter et al. (1990), Kensil et al., Marciani et al., and Uemura et al. in view, inter alia, of the mode of conjugation recited in claim 113, i.e., between the ganglioside derivative and the Keyhole Limpet Hemocyanin, which occurs by a covalent bond through a C-4 carbon of the sphingosine base of the ceramide portion of the ganglioside derivative to the ε-aminolysyl group of the Keyhole Limpet Hemocyanin, wherein the C-4 carbon is present in a CH_2 group. [emphasis supplied]. None of the above-cited references teach or even suggest such a linkage to one of ordinary skill in this art.

Applicants contend, moreover, that Irie, et al. does not satisfy the element(s) missing from the above-discussed references, and thus does not remedy the deficiencies of those references. Irie et al. is simply cited, as noted in the Office Action, for its teaching that the ganglioside GM2 is found on or in tumors of a variety of histological types, including melanoma and breast carcinomas. There is no teaching or suggestion in Irie et al. as to the claimed mode of conjugation as presently recited in all of the independent claims, including claim 113 from which claim 114 depends as noted above.

Accordingly the references as applied to claims 97-99, 101-111 and 115-118 above and further in view of Irie et al. (U.S. Patent No. 4,557,931) do not teach, suggest or disclose

applicants' claimed invention and therefore the combination does not render obvious the claimed invention. Applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Additional support for the patentability of claims 97-99, 101-111, 113-118 is provided by the disclosure of several publications, which provide evidence of unexpected immunobiological results achieved with the use of compositions as recited in the subject claims. Further with regard to those claims, applicants note that the independent claims 97, 111 and 113 have each been amended in subparagraph (a) to recite only the GM2 ganglioside, and to delete the recitation of the GD2 ganglioside. These amendments are not for the purpose of overcoming the prior art, but rather they have been made to prevent any overlap with claims of one or more related applications to the present case.

Of particular interest is a review article by P. Livingston, Ganglioside Vaccines With Emphasis on GM2, Seminars in Oncology, Vol. 25, no.6 (December), 1998, pp. 636-645, attached hereto as **Exhibit B**. The article states, at p. 641 (in col. 1, ¶1), that:

> Keyhole limpet hemocyanin (KLH) was the best of the six immunogenic carrier molecules tested in the mouse, the method of conjugation was crucial, and a potent immunologic adjuvant was required.
> ...A variety of different carriers and adjuvants have also been tested with gangliosides GM2, GD2 and fucosyl GM1[43,56]. In each case, the ganglioside covalently attached to KLH via the ceramide moiety

plus QS21 induced the highest titers of IgM and IgG antibodies.

The particular conjugation (between the ganglioside and the KLH) used with the present invention is described in detail in Helling et al., Cancer Research, Col 54:197-203 (1994) (using GD3 as the ganglioside derivative). A copy of the subject reference is attached hereto as **Exhibit C**. The relevant disclosure is found at p. 198, col.1, ¶5, i.e. "GD3 Conjugate Preparation", and in Fig. 1 on p. 199.

Additional disclosures relating to the claimed conjugation arrangement is found in Helling et al., Cancer Research, Vol. 55:2783-2788 (1995), attached as **Exhibit D**, wherein GM2 is used as the ganglioside derivative (see, e.g., p. 2783, col. 1, ¶2). According to the reference:

> Briefly, the conjugation procedure involved ozone cleavage of the ceramide double bond of GM2, introduction of an aldehyde group, and conjugation to aminolysyl groups of KLH by reductive animation.

As is seen from the teachings of the present application, of which both Messrs. Livingston and Helling are co-inventors, use of the conjugation procedure as outlined in the reference above results in conjugation of the ganglioside to the KLH through a C-4 carbon of the sphingosine base of the ceramide portion of the ganglioside derivative (e.g., GM2) to the ε-aminosyl group of the KLH, wherein the C-4 carbon is present in a CH_2 group (i.e., and not as a C=0 group as disclosed in the Liane et al. reference cited in combination to reject applicants' claims).

Further to the above, in clinical trials melanoma patients vaccinated with GM2-KLH and QS21, made using the conjugation procedure described and claimed in the present application, produced high titre IgM and IgG antibodies specific for GM2. Moreover, in at least one-half of the patients, the anti-GM2 antibody response persisted for more than 5 ½ months. Support for this is found, e.g., in Table 2 of Exhibit A (at p. 640), Table 2 of Exhibit C (at p.2787), as well as in Chapman, et al; Clinical Cancer Research, Vol 6:874-879 (March 2000), attached hereto as **Exhibit E**.

As these cited references provide clear and unambiguous evidence of unexpected improvements in immunological results achieved by the composition and methods of applicants' presently pending claims, and further as the scope of the subject claims is commensurate with the evidence provided thereby, applicants submit that this evidence clearly supports an allowance of the subject claims over the prior art cited by the Examiner.

Applicants additionally note the statement, at §12 on p.13 of the Office Action, 'that the prior art made of record, i.e., Harlow and Lane, Antibodies-A Laboratory Manual, Chapter 6, pp. 84-85 (1988), while not relied upon is considered pertinent to applicants' disclosure. In response thereto, applicants submit that they have reviewed the cited reference and that it neither teaches nor suggests the invention as presently recited in the claims, whether taken, alone or in combination with any other(s) of the cited references.

Supplemental Information Disclosure Statement

In compliance with their duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following reference, which is listed on accompanying form PTO-1449 (**Exhibit F**), a copy of which is attached hereto as **Exhibit G**.

Price, V.L., U.S. Patent No. 5,616,477, issued April 1, 1997, filed July 7, 1994. (Exhibit G).

This reference was cited in an Office Action dated September 7, 1999 in a related application (Serial No. 08/481,809) to the present application. Applicants maintain that the subject reference neither discloses nor suggests the invention claimed in the present application, whether viewed alone or in combination with any of the other cited references.

A fee of ONE HUNDRED EIGHTY DOLLARS ($180.00) is believed due for submission of this Information Disclosure Statement. Authorization is hereby provided to charge the required fee to Deposit account No. 03-3125.

Summary

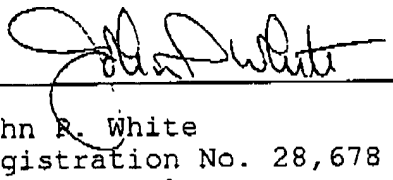
For all of the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowances of the now pending claims, i.e., claims 97, 101-111 and 113-118.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' attorney

invites the Examiner to telephone at the number provided below.

A $460.00 fee for a three-month extension of time, together with a $180.00 fee for submission of the Information Disclosure Statement, for a total of SIX HUNDRED FORTY DOLLARS ($640.00) is deemed necessary in connection with the filing of this response. Authorization is hereby given to charge the amount of the required fee to Deposit Account No. 03-3125.

Respectfully submitted,



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